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EASTERN DIVISION**

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Track Three Cases

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**DECLARATION OF STEVEN N. HERMAN IN SUPPORT OF THE PHARMACY
DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS
AND TESTIMONY OF DR. KATHERINE KEYES**

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Patterns of major depression and nonmedical use of prescription opioids in the United States

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Abstract

Introduction—Recent epidemiologic studies have shown that nonmedical use of prescription opioids (NMUPO) and major depression frequently co-occur. Comorbid forms of drug use and mental illness such as NMUPO and depression pose a greater disease burden than either condition alone. However, sociodemographic and substance use differences between individuals with either NMUPO or depression and those with comorbid conditions have not yet been fully investigated.

Methods—Data came from the 2011 and 2012 National Survey on Drug Use and Health (NSDUH). Adolescents and adults were examined independently because of differences in screening for major depressive episodes (MDE). Weighted multinomial logistic regression investigated differences between persons with either past-year NMUPO (4.0%) or MDE (5.5%) and those with comorbid NMUPO and MDE (0.6%), compared to persons with neither condition.

Results—Females were more likely than males to report either MDE-alone and comorbid NMUPO and MDE, whereas adult men were marginally more likely to report NMUPO-alone (not significant among adolescents). Polydrug use and alcohol use disorders were more pronounced among those with comorbid NMUPO and MDE than persons with either NMUPO-alone or MDE-

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Contributors

DS Fink had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Fink, Martins, and Hu developed the study concept and design. Fink, Cerdá, Keyes, Marshall, Galea, and Martins contributed to the analysis and interpretation of the data. Fink, Hu, and Martins drafted the manuscript. All authors provided a critical revision of the manuscript for important intellectual content and approved the final version of the manuscript.

Conflict of Interest

No conflict declared

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alone. Persons with independent and comorbid NMUPO and MDE were more likely to report lower income and unemployment versus employment.

Conclusions—This study found that independent and comorbid NMUPO and MDE were disproportionately clustered with burdens of lower socioeconomic position, suggesting that a population-based approach to address NMUPO would target these social determinants of health, whereas a highrisk approach to prevention should be tailored to females experiencing MDE symptoms and polydrug users.

Keywords

addiction; illegal drug use; major depressive disorder; nonmedical use of prescription opioids; polydrug use

1. INTRODUCTION

Recent epidemiologic studies have shown that nonmedical use of prescription opioids (NMUPO) and major depression frequently co-occur (Becker et al., 2008; Goldner et al., 2014; Martins et al., 2012). Comorbid forms of drug use and mental illness such as NMUPO and depression pose a greater disease burden than either condition alone, as such cases are more likely to experience more severe psychiatric symptoms (Kessler, 2004), rehospitalization (Appleby et al., 2001), incarceration (Hawthorne et al., 2012), and suicidal behaviors (Effinger and Stewart, 2012). Although nonmedical users of prescription opioids share many sociodemographic and behavioral characteristics with those who experience major depression (younger age, lower annual household income, and other substance use disorders, for example; Becker et al., 2008; Martins et al., 2012), these populations differ on other factors (sex, for example; Martins et al., 2012). The identification of characteristics that are specific to cases of comorbid NMUPO and major depressive episodes (MDE) can inform more effective intervention efforts tailored to this high-risk group. However, to our knowledge, no study has investigated the similarities and differences of populations who report NMUPO in the presences or absence of major depression.

Major depressive episodes and NMUPO are independently related to several of the same sociodemographic and substance use behaviors, including: age (Becker et al., 2008; Pratt and Brody, 2014; Wu et al., 2010), sex (Becker et al., 2008; Pratt and Brody, 2014; Wu et al., 2010), marital status (Becker et al., 2008; Riolo et al., 2005; Wu et al., 2010), and legal and illegal substance use (Becker et al., 2008). Although these risk factors are largely similar in the direction and magnitude of association with each MDE and NMUPO, certain risk factors differ. For example, whereas men are more likely than women to report NMUPO (Becker et al., 2008), women are more likely to have MDE (Hasin et al., 2005). Empirically it is very difficult to disentangle these various risk factors for MDE alone, NMUPO alone, and comorbid MDE and NMUPO. However, a study can estimate the relative frequency of differential factors to investigate the population profiles of persons with independent and comorbid NMUPO and MDE.

In the current study, we analyzed data from a nationally representative sample of the general U.S. population to identify similarities and differences among these populations that may

inform more tailored efforts to reduce NMUPO and related harm. Since MDE and NMUPO have similar risk factors—such that age, sex, marital status, education, and substance use are associated with major depression (Pratt and Brody, 2014; Riolo et al., 2005) and also NMUPO (Becker et al., 2008; Wu et al., 2010), we focused our investigation on factors previously shown to be related to both NMUPO and MDE. As such, if evidence suggests that sociodemographic and substance use factors are similar among persons reporting NMUPO-alone and those with comorbid NMUPO and MDE, then more global interventions should be implemented to reduce both NMUPO and MDE. Whereas, the identification of distinct associated factors for independent and comorbid NMUPO and MDE, suggests that intervention efforts should be more tailored to identify those at the highest risk.

2. METHODS

2.1. Sample

We used data from the National Survey of Drug Use and Health (NSDUH), conducted in 2011 and 2012. As described in more detail elsewhere (SAMHSA, 2013, 2012), the NSDUH is an ongoing annual national survey that assesses tobacco use, alcohol use and disorders, illicit drug use and disorder, and mental health symptoms in the US. The NSDUH respondents are selected from an independent multistage area probability sample of each of the 50 States and District of Columbia, yielding a nationally-representative sample of the noninstitutionalized US citizen population aged 12 years and older. After selection of potential study respondents, study trained interviewers explained all study procedures to respondents, including assurances to strict confidentiality of personal responses, obtained informed consent, and administered interviews using computer-assisted personal interviewing (CAPI) and audio computer-assisted self-interviewing (ACASI). The combined use of CAPI with ACASI are employed to increase the validity of self-reported data by providing a confidential means for the interviewees to respond to sensitive questions about illicit drug use and other behaviors (Biondo and Chilcoat, 2014; SAMHSA 2012, 2013a).

Starting in 2011, post-stratification weights were applied to adjust the NSDUH data to the distribution of the US population projections from the 2010 census. Therefore, we restricted our analysis to data from the 2011 (n = 58,397) and 2012 (n = 55,268) NSDUH public use files to assure the samples were weighted to comparable population estimates and to ensure that concatenating the data would not compromise its integrity. Since the NSDUH employs separate depression screeners for adolescents (12-17 years) and adults (18+years), we stratified the total sample into two groups at 18 years (i.e., 12-17, 18+). The final datasets included survey responses from 36,663 adolescent and 77,002 adult respondents. The weighted response rates for 2011 and 2012 were 73% and 74% respectively.

2.2. Measures

2.2.1 Past-year nonmedical use of prescription opioids (NMUPO)—Past-year NMUPO was determined through a three-stage process. First, the respondents were asked whether they have ever used “any form of prescription pain reliever that were not prescribed for you or that you took only for the experience or feeling they caused.” Second, respondents were presented with pictures and names of different types of prescription

opioids (e.g., Darvocet, Percocet, Vicodin) and asked if they had ever used them nonmedically (e.g., “Have you ever, even once, used Darvocet, Darvon, or Tylenol with codeine that was not prescribed for you or that you took only for the experience or feeling it caused?”; SAMHSA 2012, 2013a). Finally, respondents were asked: “How long has it been since you last used any prescription pain reliever that was not prescribed for you or that you took only for the experience or feeling it caused?” Respondents endorsing use during the preceding 12 months were classified as past-year nonmedical prescription opioid users.

2.2.2 Past-year major depressive episode (MDE)—We defined cases of major depressive episode using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 2000) criteria. The adolescent and adult MDE screeners were derived from the National Comorbidity Survey-Adolescent and National Comorbidity Survey-Replication (SAMHSA 2012, 2013a) respectively; respondents who endorsed experiencing five or more of the nine DSM-IV MDE symptoms, with at least one of these symptoms being either anhedonia (“little interest or pleasure in doing things”) or depressed mood (“feeling down, depressed, or hopeless”), for more than half the days over the course of a two-week period during their worst or more recent period in their lifetime, were determined to screen positive for MDE. Participants endorsing that at least a two-week period of the depressive symptoms occurred during the previous year determined the presence of a MDE in the past 12 months. In the survey, respondents endorsing MDE that was related to substance use, grief, or physical comorbidity respondents were still considered as having a past-year MDE (SAMHSA 2012, 2013a). Finally, we created a four-class nominal variable for past-year NMUPO and MDE, including: neither NMUPO nor MDE, NMUPO without MDE (NMUPO-alone), MDE without NMUPO (MDE-alone), and NMUPO with MDE (NMUPO+MDE).

2.2.3 Socio-demographic variables—We considered 10 potential independent variables of interest, including: self-reported sociodemographics (7 items), drug use characteristics (2 items), and population characteristics (1 item). Adolescent and adult sociodemographics included age at time of interview ([adolescents: 12-13 as reference, 14-15, and 16-17] and [adults: 18-25 and 26-34, 35 years or older as reference]), sex (male, female as reference), race/ethnicity (non-Hispanic white as reference, non-Hispanic black, non-Hispanic American Indian or Alaska Native [Native American], non-Hispanic Native Hawaiian or other Pacific Islander [Pacific Islander], non-Hispanic Asian, non-Hispanic two or more races, and Hispanic/Latino), and total annual family income in US dollars (0 to 19 999, 20 000 to 39 999, and 40 000 to 74 000, 75 000 as reference). Additional adult sociodemographics included: education (less than high school and high school or equivalent, some college or more as reference), marital status (single and previously married [widowed, divorced, or separated], married as reference), and employment status (employed as reference; unemployed and other). Drug experience characteristics included past-year drug use other than NMUPO (yes/no) and alcohol use disorder (yes/no). To determine past-year drug use other than NMUPO, respondents indicated whether they used several types of illegal drugs during the previous 12 months (yes or no), including: cocaine, heroin, inhalants, marijuana, and other nonmedical prescription drug use (e.g., stimulants, sedatives, tranquilizers). We summed the number of listed illegal drugs endorsed by the respondent

and created a binary variable to indicate the presence (versus absence) of any past-year illegal drug use other than nonmedical prescription opiates. Respondents meeting criteria for past-year alcohol abuse or dependence were classified as having an alcohol use disorder. Finally, county status (large metro as reference; small metro and non-metro) was derived from the 2010 Census data (SAMHSA 2012, 2013a).

2.3 Statistical analysis

To investigate the population profiles of persons with independent and comorbid NMUPO and major depression, we defined four mutually exclusive sub-groups on the basis of whether respondents reported past-year (i) NMUPO but not MDE (NMUPO-alone); (ii) MDE but not NMUPO (MDE-alone); (iii) NMUPO and MDE symptoms (MDE+NMUPO); or (iv) neither NMUPO nor MDE. We then examined sociodemographic and substance use factors that distinguish comorbid MDE and NMUPO profiles from persons reporting NMUPO-alone or MDE-alone in three phases. First, descriptive characteristics of the sample (i.e., prevalence and standard errors [SE]) were calculated. Cross-tabulations using chi-squared Wald F tests were used to examine past-year prevalence estimates for NMUPO-alone, MDE-alone, and NMUPO+MDE by covariates.

Second, we estimated unadjusted odds ratios (ORs) and 95% confidence intervals (CI) of each of the three categories of respondents (NMUPO-alone, MDE-alone, NMUPO+MDE) compared to the reference group without NMUPO or MDE. Multinomial logistic regression was used to examine the differences between the four categories of NMUPO and MDE with covariates.

Finally, we examined a multivariable multinomial logistic regression to estimate independent determinants (i.e., age, race/ethnicity, education, marital status, total family income, employment status, any past-year drug use, past-year alcohol use disorder) for NMUPO-alone, MDE-alone, and comorbid NMUPO and MDE groups in adults. Next, we estimated the same model, without employment and marital status, in the adolescent sample. Adjusted odds ratios (AOR) and 95% CIs were calculated. All data analysis was performed using SAS v 9.3 (SAS, Cary NC), and SUDAAN v 11 (Research triangle Institute, NC) was used to estimate standard errors using the Taylor series linearization method and to adjust for the effects of the weighting and clustering on the precision of estimates (Wolter, 1985).

3. RESULTS

3.1. Prevalence of past-year MDE and NMUPO (Figure 1)

Over twice the proportion of respondents reporting past-year NMUPO met criteria for comorbid MDE compared to persons not reporting NMUPO for both adolescents (19.9% versus 7.9%) and adults (15.2% versus 6.4%). Among adolescent and adult respondents, 5.8% (SE=0.17) and 4.5% (SE=0.13) respectively reported any past-year NMUPO, while 8.6% (SE=0.19) and 6.8% (SE=0.13) met criteria for past-year MDE. The overall prevalence of comorbid NMUPO and MDE was 1.2% (SE=0.08) and 0.7% (SE=0.04) among adolescent and adult respondents, respectively.

3.2. Sociodemographics of independent and comorbid NMUPO and MDE (Table 1)

All bivariate tests of differences were statistically significant at $p < 0.05$ among both adolescents and adults. As anticipated, a higher proportion of males (compared to females) reported NMUPO-alone, whereas about twice the proportion of women compared to men reported both MDE-alone and comorbid NMUPO+MDE. Among adults, NMUPO+MDE was significantly more common among unemployed persons and those reporting lower annual family income. Respondents endorsing any drug use other than NMUPO and meeting criteria for an alcohol use disorder were observed to have the largest differences in prevalence of sub-group membership; specifically, the frequency of alcohol use disorder was about 3 times higher among those with MDE-alone compared to those with neither MDE nor NMUPO and over 5 times higher among those with either NMUPO-alone or NMUPO+MDE.

3.3. Correlates of independent and comorbid NMUPO and MDE (Table 2)

Table 2 shows the multivariable multinomial logistic regression results of sociodemographic and behavioral characteristics that compare NMUPO-alone, MDE-alone, and NMUPO +MDE with those with neither NMUPO nor MDE. Columns 1-3 show the AOR for NMUPO and MDE in adolescents, adjusting for age, race/ethnicity, annual family income, drug use other than NMUPO, and alcohol use disorders, whereas columns 4-6 show the AOR for NMUPO and MDE in adults, adjusting for all the variables in the adolescent model and marital and employment status. Among both adolescents and adults, females were more likely than males to report MDE-alone (AOR=3.2 [adolescents]; AOR=1.9 [adults]) and NMUPO+MDE (AOR=3.7 [adolescents]; AOR=2.1 [adults]) than those without NMUPO or MDE. In addition, differences in MDE and NMUPO categories were observed across race/ethnicity, marital status, income, and employment. Asians were about half as likely as Non-Hispanic whites to report NMUPO-alone and comorbid NMUPO+MDE, and Non-Hispanic blacks were less likely than whites to report MDE-alone (adolescents and adults) and comorbid NMUPO+MDE (adults only). Among adults, never married respondents were more likely than married respondents to report NMUPO-alone (AOR=1.6; 95% CI, 1.3-1.9), MDE-alone (AOR=1.3; 95% CI, 1.1-1.5), and NMUPO+MDE (AOR=1.8; 95% CI, 1.1-2.9), whereas previously married respondents were more likely to report MDE-alone (AOR=1.5; 95% CI, 1.3-1.7) and NMUPO+MDE (AOR=2.0; 95% CI, 1.4-3.0). Finally, unemployed and lower income respondents were more likely to report MDE and NMUPO alone, and comorbid NMUPO+MDE than their respective categories.

Past-year drug use other than NMUPO and alcohol use disorder were the strongest factors associated with NMUPO-alone, MDE-alone, and NMUPO+MDE. However, the association between drug use other than NMUPO and alcohol use disorder with NMUPO+MDE was substantially stronger than the relationship between these factors with NMUPO or MDE alone, such that adult respondents that endorsed other drug use other than NMUPO and alcohol use disorder were respectively 15.9 and 4.5 times more likely to have NMUPO +MDE, 6.6 and 3.0 times more likely to report NMUPO-alone, and 2.5 and 2.7 times more likely to report MDE-alone compared to neither NMUPO nor MDE. Moreover, respondents endorsing drug use other than NMUPO and alcohol use disorder were significantly more likely to report NMUPO-alone and NMUPO+MDE, but not MDE-alone.

4. DISCUSSION

Using data from a nationally representative sample of adolescents and adults we found that sociodemographic and substance use characteristics were different for persons who reported either past-year NMUPO or MDE alone or comorbid NMUPO and MDE. Notably, compared to persons with neither condition, those with comorbid NMUPO and MDE were more likely to be female, of low annual income, not currently married, and to report an alcohol use disorder or other drug use. This suggests that intervention efforts to reduce the disease burden associated with comorbid NMUPO and MDE should focus on those at the highest risk, particularly females with major depression and persons with alcohol use disorder or illicit drug use.

Our results that women were more likely than men to screen positive for MDE, with or without past-year NMUPO, is not surprising given prior studies demonstrating that women are at an increased risk for both depression alone (Kendler et al., 2005; Piccinelli and Wilkinson, 2000) and comorbid substance use and depression (Chen et al., 2011; Kessler et al., 1997). However, underlying major depression may account for the previously inconsistent relationship between NMUPO and sex (Becker et al., 2008; Wu et al., 2008). For example, Becker et al. (2008) showed males were significantly more likely than females to report NMUPO, but this relationship became insignificant when adjusting for several covariates, one of which was depression. Thus, females with major depression may be more likely than males to use psychoactive substances, such as prescription opioids, which confounds the unadjusted relationship between sex and NMUPO.

Consistent with previous survey results, we found that the burden of NMUPO (Becker et al., 2008; Huang et al., 2006; Wu et al., 2010) and MDE (Hasin et al., 2005; Kessler et al., 2003) alone, and comorbid NMUPO and MDE (Schepis and Hakes, 2011), was greater in those with lower socioeconomic position (SEP), specifically lower household income and less employment. Decades of research have documented a higher burden of mental disorders among persons in lower SEP than among those in higher SEP (Johnson et al., 1999; Kessler et al., 1995). Two hypotheses have been proposed to explain this relationship between SEP and mental and substance use disorders, specifically social selection and social causation (Dohrenwend et al., 1992). Whereas the former explains that persons with mental disorders drift down the SES continuum (such that, the person's disorder causes their low SES), the latter posits that those with low SES develop psychopathology in response to the adversity and trauma in their environment. Irrespective of the direction of causation, the general consensus in the literature is that multiple processes, rather than a single underlying mechanism, are likely to drive this association between SEP and comorbid substance use and psychiatric disorder. Taken together, these findings suggest that intervention efforts that act on the social determinants of health, such as income distribution and family fragmentation (Cerdá et al., 2013a), can have a crosscutting effect on both NMUPO and MDE.

Other drug use and alcohol use disorders were more strongly associated with comorbid MDE and NMUPO, followed in magnitude by NMUPO alone, as compared to those with neither condition. The high prevalence of polydrug use among persons with NMUPO

observed in this study is consistent with previous literature (Connor et al., 2014). One recent study used latent class analysis (LCA) to show three clusters of polydrug use; a limited-range cluster (who use alcohol, tobacco, and marijuana), moderate-range cluster (who use amphetamines as well as drugs of the limited-range cluster), and an extended-range cluster (who use nonmedical prescription opioids and other illegal drugs; Connor et al., 2014). The combined evidence that NMUPO clusters in the most extended range of polydrug use and that the substantial majority of opioid related emergency department visits involve polydrug use (62%; CDC, 2010) and are among females (Cerdá et al., 2013c), suggests a confluence of factors that identify the potential high risk associated with comorbid NMUPO and MDE. In addition, psychiatric disorders, including major depression, are documented to increase the risk for substance abuse or dependence disorders among users (Martins and Gorelick, 2011). Therefore, longitudinal research that assesses drug use trajectories among this high-risk group will be particularly important to further inform population level interventions already enacted, such as the education of providers and patients about drug diversion (CDC, 2012) and prescription drug monitoring programs (Davis et al., 2014).

4.1. Limitations

This study should be considered within the context of five primary limitations that are consistent with all large-scale epidemiologic surveys. First, past-year NMUPO and MDE symptoms were self-reported (i.e., not determined through clinical diagnosis by a healthcare professional) and could be subject to recall bias. However, studies have shown that survey methods used here produce good reliability and validity (SAMHSA, 2010). Second, exclusion of incarcerated, institutionalized, and homeless adults limits generalizability. These exclusion criteria of potentially high-risk groups (e.g., incarcerated adults) may underestimate the prevalence of NMUPO in the US. Third, respondents may have underreported NMUPO and MDE symptoms (Biondo and Chilcoat, 2014; Eaton et al., 2000). However, methodological studies have documented the NSDUH had minimized this bias more effectively than other largescale epidemiologic surveys through the use of computer-assisted self-administered interviewing methods and visual aids (Biondo and Chilcoat, 2014; Harrison et al., 2007). Fourth, as our study is cross-sectional, we are unable to make any temporal claims about the associations between sociodemographic/behavioral characteristics and NMUPO and depression, nor explain the temporality between the onset of major depression and nonmedical use of prescription opioids. As there is substantial evidence for a bidirectional relationship between these conditions, future studies are needed to elucidate the causal partners of each major depression and NMUPO to explain the mechanisms that drive comorbidity. Finally, we did not consider statistical interaction in our model because without an explicit *a priori* hypothesis about potential interactions the increase in the potential for Type I error and the added complexity made this unfeasible. However, in the presence of interaction, an adjusted estimate provides the weighted average across levels of the interaction, which was of interest for our purposes. Nonetheless, futures studies that examine subgroup differences are recommended to improve prediction models.

4.2. Conclusions and clinical implications

Comorbid NMUPO and MDE is common, indicating that preventative education about the signs and symptoms of NMUPO combined with MDE are important for primary care and

specialists (such as, orthopaedists and rheumatologists) alike. These education efforts should include a push to increase screening for NMUPO and MDE among high-risk patients. Our analysis highlighted the complex interplay among sex, major depression, and NMUPO that has been previously underappreciated in studies. Specifically, we found that women are more likely than men to have major depression and comorbid NMUPO and major depression—a finding that has not been previously documented. In addition, we found that past-year illegal drug use other than NMUPO and alcohol use disorder were strongly associated with NMUPO-alone, MDE-alone, and, particularly, comorbid NMUPO and MDE. This finding highlights a need for interventions to target both high-risk polydrug users and population level interventions to ameliorate misuse of prescription opioids. Finally, we found that independent and comorbid NMUPO and MDE were disproportionately clustered with burdens of lower socioeconomic position (e.g., lower income, unemployment), suggesting that a population-based approach to address NMUPO in the U.S. would target these social determinants of health. Future longitudinal studies are needed to investigate the affect of depression on prescription opioid use trajectories, among both nonmedical and medical users.

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- We examined comorbid depression and nonmedical use of prescription opioids (NMUPO).
- Women were more likely than men to have depression alone, or with comorbid NMUPO.
- Polydrug use was particularly common in those with comorbid depression and NMUPO.
- Tailored interventions for females with depression and polydrug users are suggested.

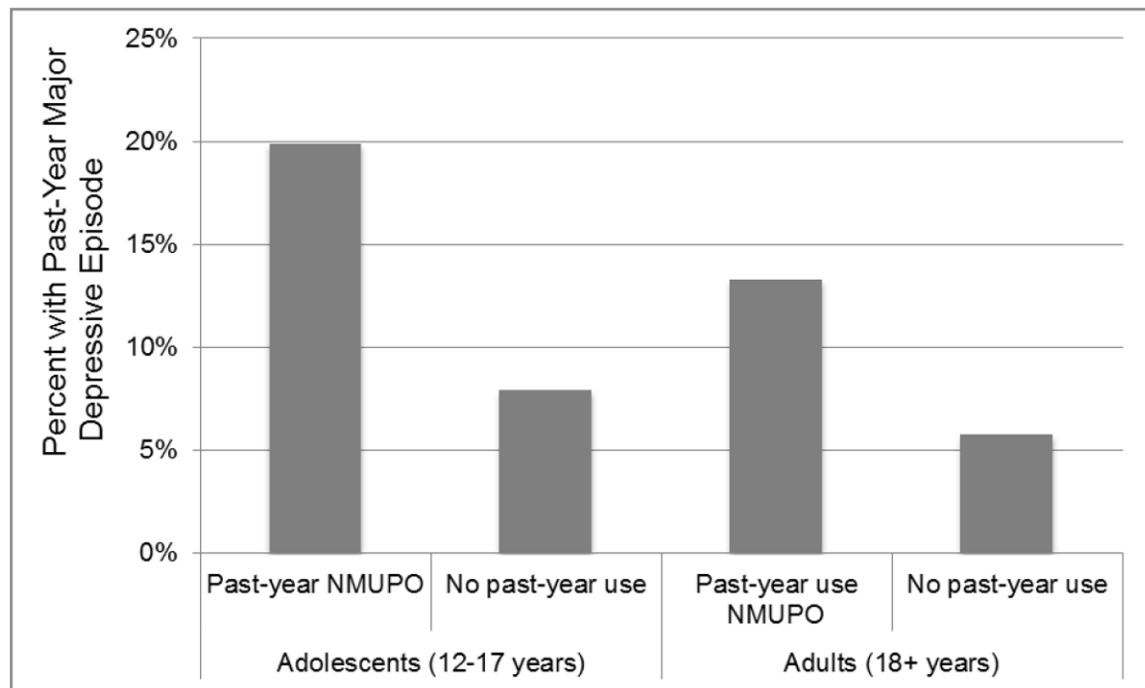


Figure 1.

Past-year major depressive episode symptoms by nonmedical use of prescription opioid (NMUPO) in adolescents (12-17 years) and adults (18 years or more), 2011-2012^a

^a Source: National Survey on Drug Use and Health, 2011-2012. Percentages are weighted to be nationally representative.

Sociodemographic and behavioral characteristics of adolescents (12-17 years) and adults (18+ years) subdivided by nonmedical prescription opioid use (NMUPO) and major depression episode (MDE) in the past-year, NSDUH^a, 2011-2012

Table 1

Characteristic	Sample, wt% (SE) ^{a,c}									
	Adolescents (n = 36,663)					Adults (n = 77,007)				
	No NMUPO, No MDE (n = 31,683)	NMUPO, No MDE (n = 1,738)	MDE, No NMUPO (n = 2,809)	NMUPO, MDE (n = 433)	p-value	No NMUPO, No MDE (n = 71,540)	NMUPO, No MDE (n = 4,591)	MDE, No NMUPO (n = 5,313)	NMUPO, MDE (n = 871)	p-value
Age, in years					<0.0001					
12-13	34.4 (0.4)	16.4 (1.0)	18.4 (1.1)	12.1 (2.2)						
14-15	33.4 (0.4)	31.4 (1.5)	36.4 (1.3)	32.2 (3.5)						
16-17	32.2 (0.4)	52.2 (1.5)	45.2 (1.2)	55.7 (3.2)						
18-25						13.7 (0.2)	32.6 (1.0)	17.0 (0.6)	33.0 (2.3)	<0.0001
26-34						15.1 (0.2)	26.3 (1.3)	16.9 (0.7)	26.3 (2.3)	
35+						71.3 (0.3)	41.1 (1.5)	66.1 (0.8)	40.6 (2.8)	
Sex					<0.0001					<0.0001
Male	53.4 (0.4)	54.0 (1.6)	26.9 (1.0)	25.8 (2.9)		48.7 (0.3)	58.1 (1.5)	34.3 (1.0)	40.1 (3.4)	
Female	46.6 (0.4)	46.0 (1.6)	73.1 (1.0)	74.3 (2.9)		51.3 (0.3)	41.9 (1.5)	65.7 (1.0)	59.9 (3.4)	
Race/Ethnicity					<0.0001					<0.0001
Not Hispanic or Latino										
White	55.1 (0.5)	56.3 (1.7)	57.1 (1.3)	63.4 (3.1)		66.5 (0.4)	67.3 (1.3)	71.9 (1.1)	78.2 (2.3)	
Black	14.3 (0.4)	14.6 (1.1)	12.0 (0.9)	11.8 (2.6)		11.5 (0.3)	11.4 (1.0)	10.2 (0.6)	6.5 (1.2)	
Native American	0.6 (0.05)	0.8 (0.2)	0.6 (0.2)	0.8 (0.5)		0.6 (0.03)	1.0 (0.2)	0.7 (0.2)	0.8 (0.3)	
Pacific Islander	0.3 (0.04)	0.2 (0.07)	0.3 (0.2)	0.4 (0.3)		0.4 (0.04)	0.2 (0.05)	0.5 (0.3)	0.3 (0.2)	
Asian	5.2 (0.2)	1.9 (0.6)	3.8 (0.6)	0.5 (0.3)		4.9 (0.2)	2.5 (0.5)	2.7 (0.4)	1.5 (0.7)	
Two or more races	2.7 (0.1)	3.6 (0.6)	3.1 (0.4)	6.2 (1.6)		1.4 (0.08)	1.4 (0.2)	1.6 (0.2)	1.4 (0.3)	
Hispanic or Latino	21.8 (0.4)	22.7 (1.4)	23.3 (1.2)	17.0 (2.1)		14.8 (0.3)	16.3 (1.1)	12.5 (0.8)	11.4 (2.0)	
Education										<0.0001
Less than high school						14.1 (0.3)	18.6 (1.0)	14.7 (0.8)	16.5 (2.4)	
High School or equivalent						29.9 (0.3)	31.9 (1.3)	28.0 (1.1)	34.0 (2.7)	
Some college or more						56.0 (0.3)	49.5 (1.1)	57.3 (1.1)	49.4 (2.9)	
Marital status										<0.0001
Never married						25.2 (0.3)	52.1 (1.6)	32.8 (0.8)	54.1 (2.7)	
Married						54.6 (0.4)	33.3 (1.4)	41.2 (1.2)	24.4 (2.9)	

Characteristic	Sample, wt% (SE) ^{a,c}									
	Adolescents (n = 36,663)					Adults (n = 77,007)				
	No NMUPO, No MDE (n = 31,683)	NMUPO, No MDE (n = 1,738)	MDE, No NMUPO (n = 2,809)	NMUPO, MDE (n = 433)	p-value	No NMUPO, No MDE (n = 71,540)	NMUPO, No MDE (n = 4,591)	MDE, No NMUPO (n = 5,313)	NMUPO, MDE (n = 871)	p-value
Previously married						20.2 (0.3)	14.6 (1.1)	26.0 (1.1)	21.5 (2.9)	
Employment status										
Employed full-time						64.4 (0.3)	71.8 (1.3)	53.8 (1.1)	57.9 (3.0)	<0.0001
Unemployed						7.2 (0.2)	13.4 (0.7)	11.1 (0.8)	16.8 (2.4)	
Other						28.4 (0.4)	14.8 (1.1)	35.2 (1.2)	25.3 (2.5)	
Annual family income, US \$										
0 to 19 999	17.5 (0.4)	22.6 (1.4)	19.2 (1.0)	21.2 (2.3)	<0.0001	18.1 (0.3)	23.9 (1.2)	29.8 (1.2)	31.2 (2.3)	<0.0001
20 000 to 39 000	20.4 (0.4)	22.6 (1.4)	21.3 (1.1)	28.2 (2.8)		21.9 (0.3)	24.6 (1.3)	22.2 (0.9)	28.3 (2.5)	
40 000 to 74 000	26.6 (0.4)	28.3 (1.3)	26.7 (1.1)	23.6 (2.4)		27.8 (0.3)	26.4 (1.0)	24.5 (1.1)	24.9 (2.2)	
75 000 +	35.3 (0.5)	26.6 (1.4)	32.7 (1.3)	27.1 (2.8)		32.3 (0.4)	25.0 (1.3)	23.6 (1.1)	15.7 (2.3)	
County status										
Large metro	54.0 (0.6)	51.8 (1.7)	54.8 (1.0)	48.2 (3.6)	0.03	53.5 (0.5)	54.6 (1.4)	49.8 (1.2)	52.0 (3.2)	0.0002
Small metro	30.4 (0.6)	31.7 (1.5)	29.2 (1.2)	39.0 (3.2)		30.5 (0.6)	31.1 (1.2)	33.8 (1.2)	35.7 (3.1)	
Nonmetro	15.5 (0.4)	16.5 (1.0)	16.0 (1.1)	12.8 (1.8)		16.0 (0.4)	14.3 (1.1)	16.4 (0.8)	12.3 (1.5)	
Any drug use other than NMUPO ^d										
Yes	2.2 (0.1)	24.4 (1.6)	6.3 (0.6)	36.6 (3.2)	<0.0001	1.2 (0.1)	15.5 (0.8)	4.1 (0.4)	29.5 (2.5)	<0.0001
No	97.8 (0.1)	75.6 (1.6)	93.7 (0.6)	63.5 (3.2)		98.8 (0.1)	84.5 (0.8)	95.9 (0.4)	70.5 (2.5)	
Alcohol use disorder										
Yes	2.3 (0.1)	17.1 (1.3)	7.3 (0.7)	29.8 (2.9)	<0.0001	5.5 (0.1)	24.6 (1.2)	14.1 (0.7)	35.1 (3.0)	<0.0001
No	97.8 (0.1)	82.9 (1.3)	92.8 (0.7)	70.2 (2.9)		94.5 (0.1)	75.4 (1.2)	85.9 (0.7)	64.9 (3.0)	

^a NSDUH = National Survey on Drug Use and Health^b wt% = weighted percentage^c SE = standard error^d Other drugs include cocaine, heroin, inhalants, marijuana, and other nonmedical prescription drug use (stimulants, sedatives, tranquilizers)

Table 2

Multinomial logistic regression result of sociodemographic and behavioral characteristics with past-year nonmedical use of prescription opioids (NMUPO) and major depression episode (MDE) categories in a community sample of adolescents (12-17 years) and adults (18+ years), adjusted odds ratio (aOR) and 95% confidence intervals (CI), NDSUH^a, 2011-2012

	aOR (95% CI)					
	Adolescents (12-17 years)			Adults (18 or more years)		
	NMUPO, No MDE ^b	MDE, No NMUPO ^b	NMUPO, MDE ^b	NMUPO, No MDE ^b	MDE, No NMUPO ^b	NMUPO, MDE ^b
Demographics						
14-15 vs. 12-13 years	1.7 (1.4-2.1)	2.0 (1.7-2.3)	2.1 (1.2-3.4)			
16-17 vs. 12-13 years	2.4 (2.1-2.8)	2.5 (2.1-2.9)	2.9 (1.9-4.6)			
18-25 vs. 35+ years				2.0 (1.7-2.4)	0.9 (0.8-1.0)	1.6 (1.1-2.3)
26-34 vs. 35+ years				2.1 (1.7-2.5)	1.1 (1.0-1.3)	2.1 (1.4-3.0)
Women vs. Men	1.1 (0.9-1.2)	3.2 (2.9-3.5)	3.7 (2.7-5.2)	0.9 (0.8-1.0)	1.9 (1.7-2.1)	2.1 (1.5-2.8)
Non-Hispanic Black vs. Non-Hispanic White	0.9 (0.7-1.1)	0.8 (0.6-0.9)	0.7 (0.4-1.1)	0.7 (0.6-0.9)	0.6 (0.5-0.7)	0.3 (0.2-0.4)
Native American vs. Non-Hispanic White	1.2 (0.7-2.0)	0.9 (0.4-2.0)	0.8 (0.3-2.8)	1.3 (0.8-2.2)	0.8 (0.5-1.4)	0.7 (0.3-1.6)
Pacific Islander vs. Non-Hispanic White	0.4 (0.2-1.0)	0.6 (0.2-1.7)	0.5 (0.1-3.2)	0.4 (0.2-0.8)	1.1 (0.3-3.8)	0.5 (0.1-3.0)
Asian vs. Non-Hispanic White	0.4 (0.2-0.7)	0.7 (0.5-1.0)	0.1 (0.03-0.4)	0.5 (0.3-0.7)	0.5 (0.4-0.7)	0.3 (0.1-0.7)
Two or more races vs. Non-Hispanic White	1.2 (0.8-1.7)	1.1 (0.8-1.4)	1.7 (1.0-3.0)	0.8 (0.6-1.0)	0.9 (0.7-1.2)	0.6 (0.3-1.0)
Hispanic vs. Non-Hispanic White	0.9 (0.7-1.1)	1.0 (0.9-1.2)	0.6 (0.4-0.8)	0.8 (0.7-1.0)	0.7 (0.6-0.8)	0.5 (0.3-0.7)
Never married vs. married				1.6 (1.3-1.9)	1.3 (1.1-1.5)	1.8 (1.1-2.9)
Previous married vs. married				1.2 (1.0-1.5)	1.5 (1.3-1.7)	2.0 (1.4-3.0)
Employment status						
Unemployed vs. employed				1.2 (1.0-1.4)	1.5 (1.2-1.8)	1.6 (1.1-2.3)
Other employment vs. employed				0.6 (0.5-0.7)	1.3 (1.1-1.4)	1.0 (0.8-1.4)
Annual family income, US\$						
<20,000 vs. 75,000	1.7 (1.4-2.0)	1.3 (1.1-1.5)	1.7 (1.2-2.6)	1.3 (1.1-1.6)	1.7 (1.5-2.0)	2.2 (1.4-3.2)
20,000-39,000 vs. 75,000	1.5 (1.2-1.9)	1.2 (1.0-1.4)	2.0 (1.5-2.8)	1.3 (1.1-1.6)	1.2 (1.0-1.4)	2.1 (1.3-3.4)
40,000-74,000 vs. 75,000	1.4 (1.2-1.7)	1.1 (1.0-1.3)	1.2 (0.9-1.8)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	1.6 (1.1-2.4)
Substance use characteristics						
Any drug use other than NMUPO ^c	7.9 (6.2-1.0)	2.2 (1.7-2.8)	12.4 (8.4-18.3)	6.6 (5.6-7.8)	2.5 (2.0-3.1)	15.9 (11.0-22.8)
Alcohol use disorder	3.4 (2.5-4.6)	2.2 (1.8-2.8)	5.3 (3.6-7.8)	3.0 (2.6-3.5)	2.7 (2.4-3.1)	4.5 (3.1-6.4)

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Note: Bold values indicate adjusted odds ratios significant at level of <0.05

^bNSDUH = National Survey of Drug Use and Health

^bReference category: No past-year use of prescription opioids or major depression episode (MDE). Results are from multinomial logistic regression model with categorical outcome (0 – Non-NMUPO without MDE, 1 – NMUPO-alone, 2 – MDE-alone, 3 – NMUPO and MDE).

^cOther drugs include cocaine, heroin, inhalants, marijuana, and other nonmedical prescription drug use (stimulants, sedatives, tranquilizers)